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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/610,313	07/05/2000	Susan Barnett	PP01631.101	4221

27476 7590 06/18/2002

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 06/18/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/610,313	Applicant(s) BARNETT ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *41* is/are withdrawn from consideration.

5)☒ Claim(s) *48,50 and 51* is/are allowed.

6)☒ Claim(s) *1-40,42-47 and 49* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *05 July 2000* is/are: a)☐ accepted or b)☒ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *11* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Final Rejection

Claims 1-40 and 42-51 are pending examination.

Applicants' traversal, the amendment to claims 4-5, 8, 21-22, 25, 29, 36, 42, 43, the addition of claims 48-51, and Exhibit A in paper no. 11 are acknowledged and considered.

Furthermore the declaration of Susan Wilson under 1.132 in paper no. 11 is acknowledged and considered.

This application contains claim 41 drawn to an invention non-elected with traverse in Paper No. 7. A complete reply to the final rejection must include cancellation of non-elected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Drawings

NOTE: In the next response, please submit a response to the PTO 498 because a PTO 498 was filed with the non-final rejection dated 9/21/01 and the applicants have not submitted proposed corrections or corrections to the drawings. If the reply to the Final Rejection does not have a response to the 498, the response will be considered non-responsive. See 37 CFR 1.85(a).

Claim Objections

Applicants assert that the amendment to claim 36 obviates this objection. See page 5. The assertion is acknowledged and is not found persuasive because claim 36 remains objected to because it should read, "wherein said composition is delivered **by** using a particulate carrier."

In addition, in view of the amended or new claims, claim 1 and new claim 49 are objected to because of the following informalities: missing a comma before the conjunction term "and". Appropriate correction is required.

The rejection under 112 written description for claim 4 is withdrawn, however, the following rejections under 112 enablement remain or apply.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-40 and 42-47 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for 1) An expression cassette comprising a polynucleotide sequence encoding a Pol polypeptide, wherein the polynucleotide sequence encoding said Pol polypeptide is set forth in SEQ ID NOs: 30, 31, or 32; 2) The expression cassette of 1, wherein said polynucleotide sequence further comprises a nucleic acid sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof; 3) A method for generating an immune response in a mammal, comprising intramuscularly administrating the expression cassette of 1 to said mammal; 4) The expression cassette of 1, further comprising one or more nucleic acids encoding one or more viral polypeptides or antigens, and does not reasonably provide enablement for the rest of the disclosure. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The invention lies in the field of producing an immunogenic composition or vaccine using an expression cassette comprising an HIV Pol polypeptide set forth in SEQ ID NOs: 30-32.

The state of the art exemplified by Gurunathan et al. indicates that the goal of developing effective vaccines for a particular disease depends on several factors:

1) Identification of a conserved antigen capable of inducing protection is an outbred population.

2) Design vaccines that can induce an appropriate qualitative and quantitative immune response.

3) Some diseases require different types of immune responses for effective primary and memory immunity (*J Immunol*, Vol. 161(9), pg. 4563, November 1998).

In addition, major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered

2) The route and time course of administration, the sites of administration, the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

3) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the subject being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson indicates that the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in a subject is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma et al., *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, in view of the state of the art, producing an immunogenic composition or vaccine using a replicant defective vector encoding a nucleotide sequence is considered unpredictable.

The application contemplates: 1) Expression assays for the synthetic coding region of Pol, Env, and Gag-protease expression cassettes; 2) In vivo immunogenicity of Gag, Pol, and Env expression cassettes using plasmid DNA carrying the synthetic Gag, Pol, and Env expression cassette; 3) DNA immunization of non-human primates by administering intradermally, mucosally, bilaterally, intramuscularly into the quadriceps using various doses of a synthetic Pol, Env, and Gag-containing plasmid; 4) In vitro expression of recombinant alphavirus vectors or plasmid containing the synthetic Gag, Pol, and Env expression cassette; 5) In vivo immunogenicity of recombinant Sindbis replicon vectors containing Gag, Env, and Pol expression cassettes in mice by using intramuscular and subcutaneous routes.

The disclosure further claims that these experiments will exhibit increased potency for induction of cytotoxic T-lymphocytes (CTL) response and humoral immune response by using the Gag, Pol, and Env expression cassettes.

The as-filed specification provides sufficient guidance for one skilled in the art to make an immunogenic composition comprising an expression cassette comprising of a polynucleotide sequence set forth in SEQ ID NOs: 30-32 and make an expression cassette further comprising a viral polypeptide or antigen selected from the group consisting of Gag, Env, vif, vpr, tat, rev, vpu, nef. In addition, the prior art and as-filed specification provide sufficient guidance for one skilled in the art to use the immunogenic composition comprising an expression cassette comprising of one the polynucleotide sequences set forth in SEQ ID NOs; 30-32 in a method of producing an immune response in a mammal by using intramuscular administration.

However, the as-filed specification does not provide sufficient description or one skilled in the art to make a sequence having at least 90% identity to any of the sequences presented as SEQ ID NO: 30-32. The specification does not provide sufficient guidance for what amino acids of any of the sequence listed above may be changed while Pol polypeptide activity is retained. Since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art to arrive at other sequences that have at least 90% sequence identity to the Pol polypeptide encoded by SEQ ID NOs: 30-32.

In addition, the state of the art and the specification do not provide sufficient guidance for claims encompassing stem cells or progenitor cell thereof comprising an expression cassette of

claim 1. One skilled in the art and considered would understand that if the expression cassette is not stably integrated into the genome of the host cell *e.g.* lymphoid cell, it would not be present after several rounds of replication. Also, one skilled in the art would understand that the development of a successful strategy for long-term gene expression in stem cells is immense (Prince, *Pathology,* Vol. 30, pp. 340, 1998). Prince teaches "the difficulties in determining the conditions to optimize stem cells division and consequently transduction, the ability to recognize and quantify successful transduction into stem cell is problematic (page 340)." Thus, in view of the specification and state of the art, the specification does not provide sufficient guidance for one skilled in the art to make and use stem cells or progenitor with the expression cassette of claim 1.

Furthermore with respect to claims encompassing a method of immunization of a subject using an immunogenic composition comprising the expression cassette comprising an HIV Pol polypeptide encoded by a polynucleotide sequence set forth in SEQ ID NOs: 30-32, the state of the state of the art for immunizing a subject against HIV and in view of the disclosure does not provide sufficient guidance for one skilled in the art to produce a therapeutically effective (partial and/or full protection and treatment) in a subject. The state of the art regarding HIV vaccines as exemplified by Nathanson et al. *The Journal of Infectious Disease*, Vol. 182, pp. 579-89, 2000) suggest that the formulation of an effective AIDS vaccine constitutes a daunting challenge for a number of reasons, including the following:

1) the ability of the virus to persist, to replicate in the face of a vigorous immune response and ultimately, to destroy the integrity of the immune system by an attack on CD4 helper T lymphocytes;
2) the question of whether partial immunity will suffice to protect vaccines against eventual disease;
3) the absence of a single clear-cut immune correlate of protection;

4) the difficulty of inducing neutralizing antibodies;
5) the necessity of defining and inducing CTL epitopes that are immunodominant for each of many different MHC class I haplotypes;
6) the question of whether a vaccine formulated on a virus of a single clade will protect against infection with viruses of other clades;
7) the question of whether an effective vaccine must induce mucosal immunity; and
8) the difficulty of developing an attenuated virus strain is immunogenic (page 586).
Furthermore, Nathanson states that 15 years have past since HIV-1 was isolated and yet the possibility of an AIDS vaccine still appears quite remote (page 579).

In view of the state of the art for producing an HIV vaccine, the as-filed specification does not provide sufficient guidance for one skilled in the art to use the expression cassettes exhibiting the contemplated biological functions as sought in the disclosure (*e.g.* under conditions that are compatible with expression of said expression cassette) in a method of immunization of a subject. The disclosure does not address what amount of expression of the Pol polypeptide is required in a subject to produce a treatment (encompasses partial/complete protection) and/or prevention (total protection) in said subject. Furthermore, the application does not provide sufficient guidance for how one skilled in the art would circumvent the immunological response of subject for a sufficient time for the Pol polypeptide to be expressed at a sufficient amount to produce a therapeutic response in the subject. This is important because the modulation of the expression level is necessary for each polypeptide to elicit a desired immune response without modifying or shutting the down host cell function and causing negative effects similar to those of traditional vaccines (Azevedo et al., *Brazilian Journal of Medical and Biological Research*, Vol. 32, page 152, 1999). In addition, as-filed specification does not address the concern with repeated administration of an immunogenic vector since repeated administration would cause decrease expression of the desired Pol polypeptide. Also, it would take one skilled in the art an undue amount of experimentation to determine how to target

a specific tissue, which requires that the vector avoids degradation in the blood stream and integrates into the desired targeted tissue or cells. In addition, the specification does not provide sufficient guidance for one skilled in the art to determine whether the translation product produced is similar to the native Pol polypeptide encoded by polynucleotide sequences set forth in SEQ ID NOs: 30-32 after the gene is transcribed from the expression cassette in a cell because sometimes proteins are often inactive or otherwise possess different properties from the native protein due to protein folding after expression in a subject's (*e.g.* mice, primate, human, etc.) cells. If the polypeptide produced in the cells is different from the Pol polypeptide set forth in polynucleotides sequences SEQ ID NOs: 30-32 then the modified polypeptides might not function as indicated by the claimed embodiment (*e.g.* method of immunization of a subject using an immunogenic composition comprising a sequence having at least 90% sequence identity to either SEQ ID NOs: 30-32 into said subject under conditions that are compatible with expression of said expression cassette in said subject).

Furthermore, the examples in the as-filed specification appear to be prophetic examples due to the wording of the each example (*e.g.* verbs are in present tense form). In view of the unpredictability of gene therapy and the doubts expressed in the art of record, one skilled in the art would not be able to reasonably correlate that the examples set forth in the as-filed specification are working examples. In view of these factors (state of the art for gene therapy, skill in the art of producing and HIV vaccine, and prophetic examples) and the concerns listed above, it is not apparent to one skilled in the art how to reasonably extrapolate experiments comprising prophetic examples to any method of immunization of a subject comprising, an

immunogenic composition comprising an expression cassette, comprising a polynucleotide sequence encoding a synthetic HIV Pol polypeptide set forth in SEQ ID NOs: 30-32.

In addition to the doubts expressed in Anderson, Nathanson, and Verma, the state of art exemplified by McCluskie et al. (*Molecular Medicine*, 5, pp. 287-300, 1999) teach that "the realization that results in mice often do not predict the situation in humans has also led to a large number of DNA vaccine studies in non-human primates", that "IM injection of plasmid DNA vaccines, while highly immunogenic in mice...was found only to be relatively so in chimpanzees..., and especially not all in Aotus monkeys"' and that "it is probably safe to say that any vaccine that works in a human will work in a mouse, but note necessarily vice-versa" (page 296, column 2, second and third paragraphs). In addition, McCluskie et al. teach that "although non-human primate models are frequently used for development and testing of human vaccines, it is not clear how predicative they will be in the case of DNA vaccines where efficacy, by virtue of the requirement first to transfect cells and express the antigen, relies on many factors other than immunological reponses to the antigen" (page 297, column 1).

Thus, it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of vertebrate to the full scope of the claimed invention that would generate a treatment (encompasses partial/complete protection) and/or prevention (total protection) in any subject against any subtype of HIV. Even if the specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, encompassing any host (*e.g.*, snake, bird, fish, mammal, etc.) particularly given that there is no

vaccine generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record.

With respect to vaccination methods encompassing routes of administration, e.g., intranasally and intramuscular, the state of the art exemplified by McCluskie teaches that the route of delivery of the DNA vaccine can have an impact on the efficiency of transfection as well as the types and location of cells transfected, and thus potentially on the nature of the immune response (pg. 295). In addition, McCluskie teaches that many different routes have been shown to be effective for DNA delivery in mice; however, few studies have compared responses obtained with different routes using the same antigen-expressing DNA, dose, and immunization schedule. There have been even fewer studies to compare routes of administration in non-human primates (pg. 295).

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable the claimed invention 1-4, listed above. One would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the application's disclosure, the unpredictability of gene therapy and developing effective HIV vaccines encompassing any subject including any mammal for a protective effect and/or treatment. In addition, the prophetic examples as provided in the specification do not reasonably extrapolate to the full scope of the claimed invention given that there is no evidence that the prophetic examples are a general phenomenon.

Applicants traverse the rejection under 112 enablement for the following reason(s): claims 22-47 are directed to a method for generating an immune response and none of these claims recite "vaccine composition" or "method of treating (or vaccination against" HIV, rather they are drawn to compositions and methods for generating an immune response in a mammal; As is well-known and described, for example on page 15 of the specification, the generation of an immunological response does not necessarily provide protection and/or therapy; Applicants are not required to establish whether these immunological responses are protective or therapeutic; Applicants direct the Examiner's attention to Example 4-7 and attached Exhibit A that demonstrates the claimed expression constructs induce an immune response in a mammal when made, administered and tested for immunogenicity following the teaching of the specification; The references cited are a far cry away from establishing that methods of immune response to the claimed expression cassettes are not enabled by Applicants specification. See pages 8-11

In addition, applicants traverse the rejection under 112 enablement with respect to percent identity because the use of available programs for calculating identity or similarity between sequences is fully disclosed in the specification (pages 19-22). See page 12.

Furthermore, the Declaration set forth by Susan Wilson, PhD, asserts that following: the specification clearly convey to a typical scientist that the inventor had in their possession the invention of claim 4 (page 2); it was widely known how to construct expression cassettes, including vectors having two or more polypeptide-

encoding sequences (See section 2.2.3 of the as-filed specification), it would have been routine to a typical scientist working in this area in view of the teachings of the specification (page 3); the specification clearly describes how to determine those sequences having 90% sequence identity to the claimed HIV Pol-encoding sequences of SEQ ID NOs: 30-32 (See pages 19-22 and page 75 of the specification).

Applicants' traversal is acknowledged and is found partially persuasive because as stated in the last office action and re-stated above, the claimed invention is enabled for making and/or using an expression cassette comprising and HIV polypeptide selected from SEQ ID NO: 30, 31, or 32 in a method of generating an immune response in a mammal comprising intramuscularly administering the expression cassette to the mammal. However, applicants' traversal is not found persuasive for one skilled in the art to make and/or use the full scope of the claimed invention because in view of the unpredictability for one skilled in the art to make and/or use an expression cassettes comprising a nucleotide sequences having at least 90% sequence identity to the sequence presented in SEQ ID NOs: 30-32 and in view of the art of record concerning the unpredictability of making and/or using a method of immunization and the lack of guidance provided by the as-filed specification, it would take one skilled in the art an undue amount of experimentation to make and/or use the full scope of the claimed invention.

First, with respect to the starting material set forth in claims 1-7 and 22-28, the as-filed specification provides sufficient guidance for one skilled in the art to make and/or use the expression cassette comprising SEQ ID NO: 30, 31, or 32, and wherein

said polynucleotide sequence further comprises a nucleic acid sequence encoding a viral polypeptide selected from Gag, Env, vif, vpr, tat, rev, vpu, nef, and combinations thereof or cytokines. It is noted that computer programs available are considered conventional for one skilled in the art to calculate identity or similarity between sequences. However, the as-filed specification, Declaration under 1.132, and the applicants' traversal do not provide sufficient guidance for one skilled in the art to make and/or use a sequence having at least 90% sequence identity to SEQ ID NO: 30, 31, or 32 as the starting material, because they do not teach what amino acids or polynucleotides (e.g. epitopes) are considered essential to retain the Pol activity observed by SEQ ID NOs: 30-32 and to use a sequence with 90% sequence identity as the starting material in an expression cassette for generating an immune response while observing an immune response observed when using an expression cassette comprising SEQ ID NOs: 30, 31, or 32. More specifically, the as-filed specification and/or applicants' traversal and/or Declaration under 1.132 do not provide sufficient guidance and/or factual evidence for what amino acids of any of the sequence listed above may be changed while Pol polypeptide activity observed with SEQ ID NOs: 30, 31, or 32 is retained. Since the relationship of the sequence of a peptide and its tertiary structure (*e.g.* its activity) are not well understood and are not predictable (Ngo et al. The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495), it would require an undue amount of experimentation for one skilled in the art to arrive at other sequences that have at least 90% sequence identity to the Pol polypeptide encoded by

SEQ ID NOs: 30-32 and to make and/or use an expression comprising sequences that have at least 90% sequence identity to the Pol polypeptide set forth in claim 1 in a method of generating an immune response to HIV Pol polypeptide (SEQ ID NOs: 30, 31, or 32).

Furthermore, in view of the applicants assertion that other sequences can be identified using available programs for calculating identity between sequences is not found persuasive because one skilled in the art would require a polynucleotide sequence (starting material) and the search of the prior art displays that there are no sequences with at least 90% sequence identity to SEQ ID NO: 30, 31, or 32 and in view of the lack of guidance provided by the art of record, one skilled in the art would rely on the guidance provided by the as-filed specification. In view of the reasons set forth above, the disclosure does not provide sufficient for one skilled in the art to make and/or use any polynucleotide with at least 90% sequence identity to SEQ ID NO: 30, 31, or 32.

In addition, with respect to the assertion that the claimed invention is only encompassing a method of generating an immune response and not a vaccine, the as-filed specification defines "nucleic acid immunization" as the introduction of a nucleic acid molecule encoding one or more selected antigens into a host cell, for the in vivo expression of an antigen, antigens, an epitope, or epitopes (page 23). However, the art of record defines immunization" as "the protection to an individuals who have been exposed to an infectious organism or to elicit protective immunity and immunologic memory so that a subsequent exposure to the pathogenic agent will elicit a heightened immune response with successful elimination of the pathogen" (Kuby, Immunology,

2nd ed, W.H. Freeman and Company, 1994, pages 470-471). Stedman's Medical Dictionary (Williams and Wilkins, 26th ed, 1995, page 853) further defines immunization as "the protection of susceptible individuals from communicable disease by administration of a living, suspension of killed organisms, or inactivated toxin". Thus, in view of the definition of the term "immunization" by the state of the art, one skilled in the art would reasonably determine that a method of immunization for *in vivo* expression encompasses a protection of a mammal from HIV Pol.

More specifically, one skilled in the art would look for the definition of the term in the specification and on page 16 the disclosure states, "The response may serve to neutralize infectivity, and/or mediate antibody-complement, or antibody dependent cell cytotoxicity (ADCC) to provide protection to an immunized host as stated above" and on page 58 "it is readily apparent that the subject invention can be used to mount an immune response to a wide variety of antigens and hence to treat or prevent a HIV infection particularly Type C HIV infection". Therefore, a method of generating an immune response is well known to one skilled in the art, however, in view of the term "immunization" in the art record and the general definition provided by the as-filed specification (pages 16, 23, and 58), one skilled in the art would reasonable determine that the claims 1, 22, and 29-40 read on a method of treatment or protecting a mammal against HIV.

The traversal and the as-filed specification do not provide any sufficient guidance and/or factual evidence to overcome the concerns set forth by the art of record for making an expression cassette comprising SEQ ID NO: 30, 31, or 32 and

using the cassette in a method of immunization because of the reasons set forth in the enablement rejection. The traversal only asserts that the specification provides sufficient guidance for one skilled in the art to make and use the expression cassettes comprising SEQ ID NO: 30, 31, or 32 and that the applicants are not required to establish whether these immunological responses are protective or therapeutic. In view of the concerns cited above by the art of record for making and/or using a method of immunization of a subject and the lack of guidance provided by the specification, it would take one skilled in the art an undue amount of experimentation to reasonably extrapolate from generating an immune response in a subject to a method of immunization in a subject.

In addition, with respect to making and/or using any cell comprising an expression cassette comprising SEQ ID NO: 30, 31, or 32, the applicants' traversal and the as-filed specification do not provide sufficient guidance for a representative number of stem cells or progenitor cell thereof comprising an expression cassette of claim 1 because they do not address the concerns set forth in the 112 enablement rejection. One skilled in the art would understand that the development of a successful strategy for gene expression in stem cells is immense (Prince, *Pathology,* Vol. 30, pp. 340, 1998). Prince teaches "the difficulties in determining the conditions to optimize stem cells division and consequently transduction, the ability to recognize and quantify successful transduction into stem cell is problematic (page 340)." To further emphasize the unpredictability for using animal stem cells in a method for expression of a transgene set forth by Prince, the art displays pre and post-filing references showing the unpredictability of using animal stem cells; see Chu et al., J. Mol. Med, Vol. 76, 1998, pp. 184-

92, Van Tendeloo et al., Leukemia 2001, Vol. 15, pp. 523-544; Richter et al., Int. J. Hematol. Vol. 73, 162-169, 2001; Romano et al., Stem Cells, Vol. 18, pp. 19-39, 2000; Halene et al. Human Gene Therapy, Vol. 11, pp. 1259-1267, 2000. Thus, in view of the specification and the state of the art, the as-filed specification and the applicants' traversal do not provide sufficient guidance for one skilled in the art to make and/or use stem cells or progenitor thereof comprising the expression cassette set forth in the scope of enablement.

Furthermore, the traversal is not found persuasive with regard to a method of immunization in a subject, because it is not apparent as how one skilled in the art reasonably extrapolates, without undue experimentation, from the scope of mammal to the full scope of the claimed invention that would generate a treatment (encompasses partial/complete protection) and/or prevention (total protection) in any subject against any subtype of HIV. Even if the specification contemplated that a clear improvement using the synthetic expression cassettes in an immunogenic composition has been prophetically displayed in mice, it is not apparent as to how the prophetic examples are reasonably extrapolated to the full scope of the claimed invention, encompassing any host (*e.g.*, snake, bird, fish, monkey, human, etc.) particularly given that there is no immunization generation evidence showing that the prophetic examples are a general phenomenon, and given the doubts expressed in the art of record.

With respect to the traversal for claims rejected under 112 second. Applicants' traversal (see pages 12-13) is acknowledged and is found persuasive and the rejection for claims 8, 21-22, 25, 29, and 42, 43, 47 are withdrawn.

Claims 48 and 50-51 are in condition for allowance because they are free of the prior art.

Other than claims 48 and 50-51, no other claim is in condition for allowance.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
6/13/02

DAVE T. NGUYEN
PRIMARY EXAMINER